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Endocrinologist, Tauranga Hospital

Diabetes in Pregnancy - Concurrent Workshop Repeated

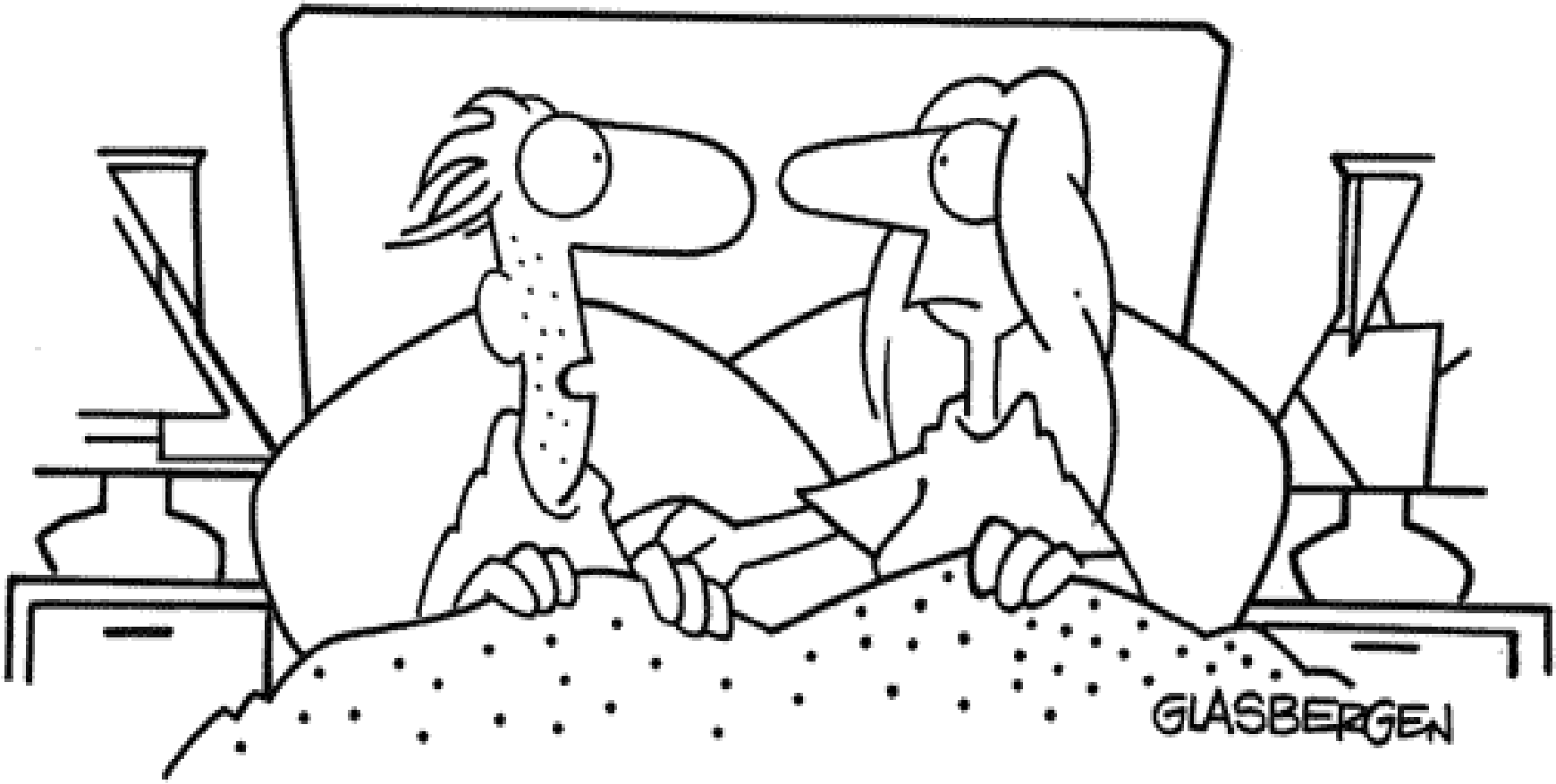
Saturday, 11 June 2011	Start 2:00pm	Duration: 55mins	Picasso
	Start 3:05pm	Duration: 55mins	Picasso

Diabetes in Pregnancy
Rotorua GP CME Meeting
June 2011

Kingsley Nirmalaraj, FRACP
Consultant Physician & Endocrinologist
Tauranga Hospital

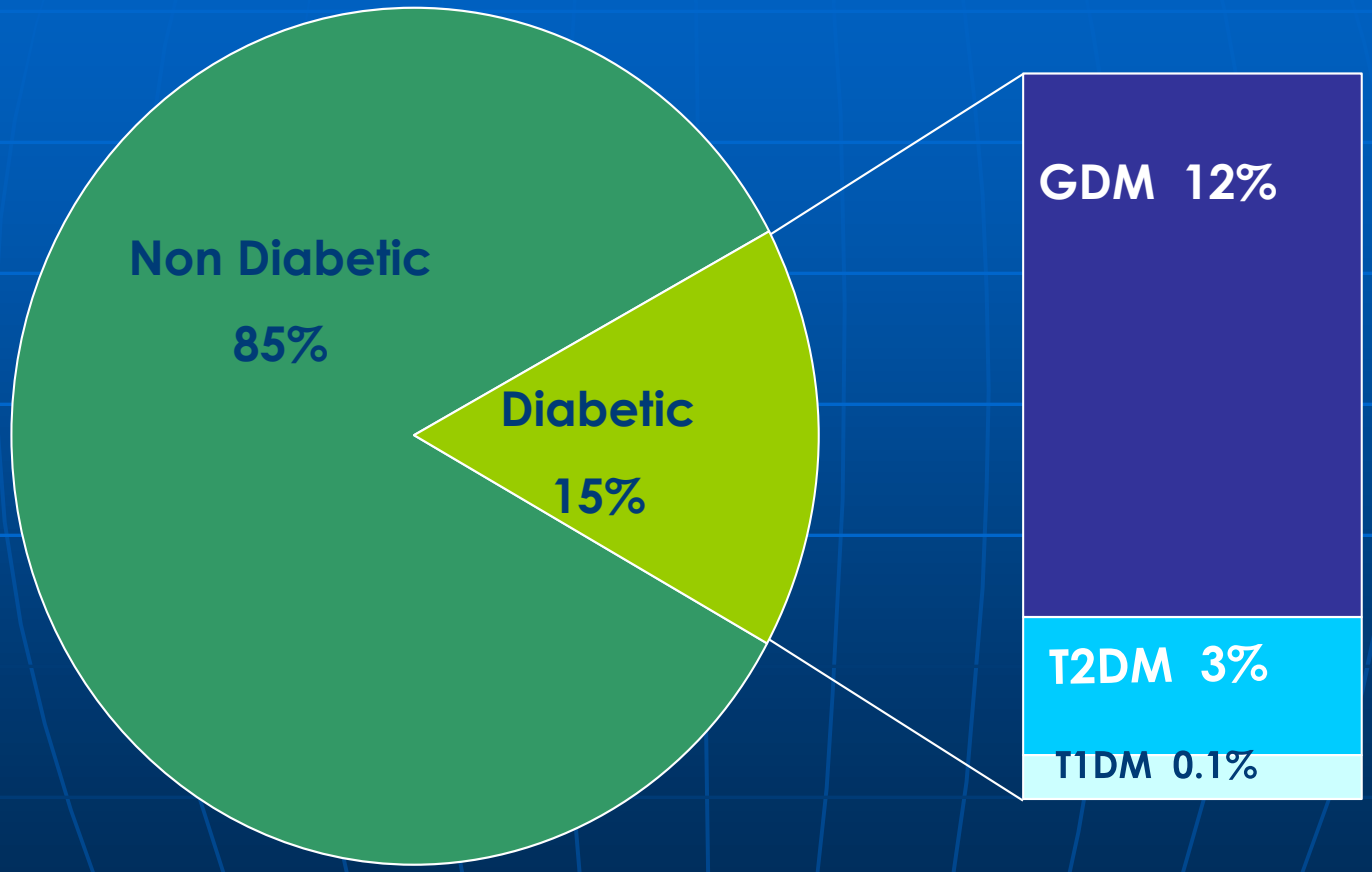
Agenda

- Types of Diabetes
- Pathophysiology
- Screening/high risk group
- Diagnostic criteria
- Glucose targets, treatment
- Pre-pregnancy counseling
- Cases



"Let's try getting up every night at 2:00 AM to feed the cat. If we enjoy doing that, then we can talk about having a baby."

Hyperglycaemia in Pregnancy



What is GDM?

Why is it important?

- Increasing diabetes prevalence
- Increasing BMI
- Increasing maternal age
- Diverse ethnicity

Glucose levels during pregnancy

Women without diabetes, mean glucose levels:

- Fasting glucose 4.2 (0.67) mmol/l
- Postprandial 1-hr 6.1 (0.89) mmol/l
  2-hr 5.4 (0.55) mmol/l
- Obese women higher than non-obese during day, but lower overnight

At what level of glucose does pregnancy risk increase??

Women become insulin resistant in pregnancy

Compensatory response balanced

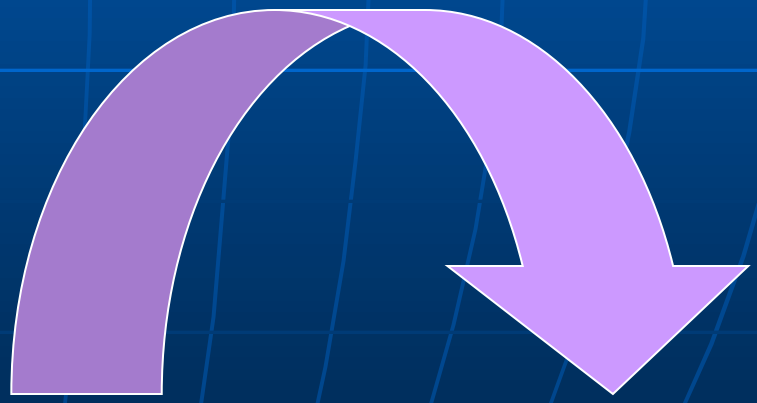
- Normal pregnancy

Compensatory response inadequate

- Gestational diabetes (GDM)

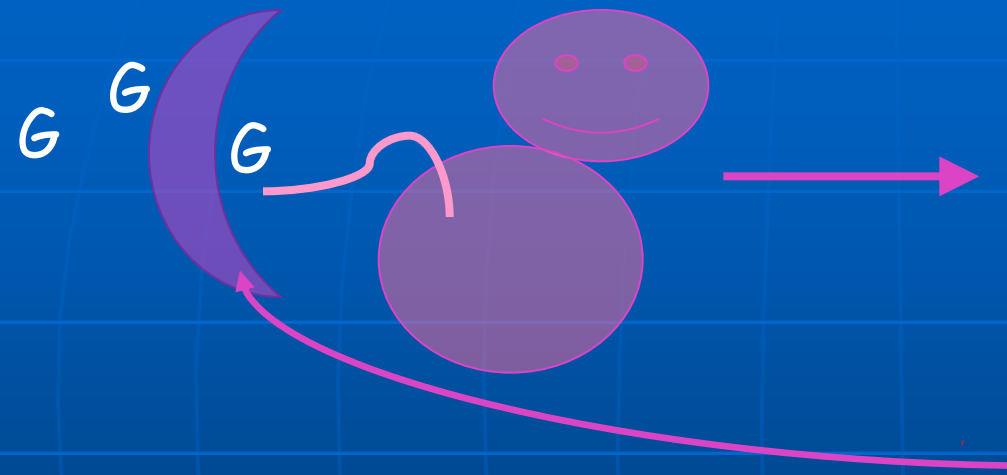
Women with pre-existing diabetes

- Affects management



Diabetes - effect on the fetus

Excess nutrition



Newborn: hypoglycaemia, respiratory distress, jaundice

Later life: obesity, type 2 diabetes ("programming")

Why is GDM important?

Mother

- Increased pregnancy risks
- Increased risk of later type 2 diabetes

Baby

- Increased pregnancy risks
- Increased newborn morbidity
- Increased risks of obesity and type 2 diabetes

Intervention improves pregnancy outcomes

Potential to improve long term outcomes

TIMELY RECOGNITION

Effect of Treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes

Caroline A. Crowther, F.R.A.N.Z.C.O.G., Janet E. Hiller, Ph.D., John R. Moss, F.C.H.S.E., Andrew J. McPhee, F.R.A.C.P., William S. Jeffries, F.R.A.C.P., Jeffrey S. Robinson, F.R.A.N.Z.C.O.G. and the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group

Consensus is lacking as to whether routine screening and treatment for gestational diabetes mellitus is warranted

This large randomized trial of the treatment of gestational diabetes demonstrated that serious perinatal complications were significantly less common among the offspring of women who received dietary advice, blood glucose monitoring, and insulin therapy as needed to maintain glycemic control than among the offspring of women who received routine care

These findings provide strong support for the implementation of screening for and treatment of gestational diabetes

N Engl J Med
Volume 352;24:2477-2486
June 16, 2005

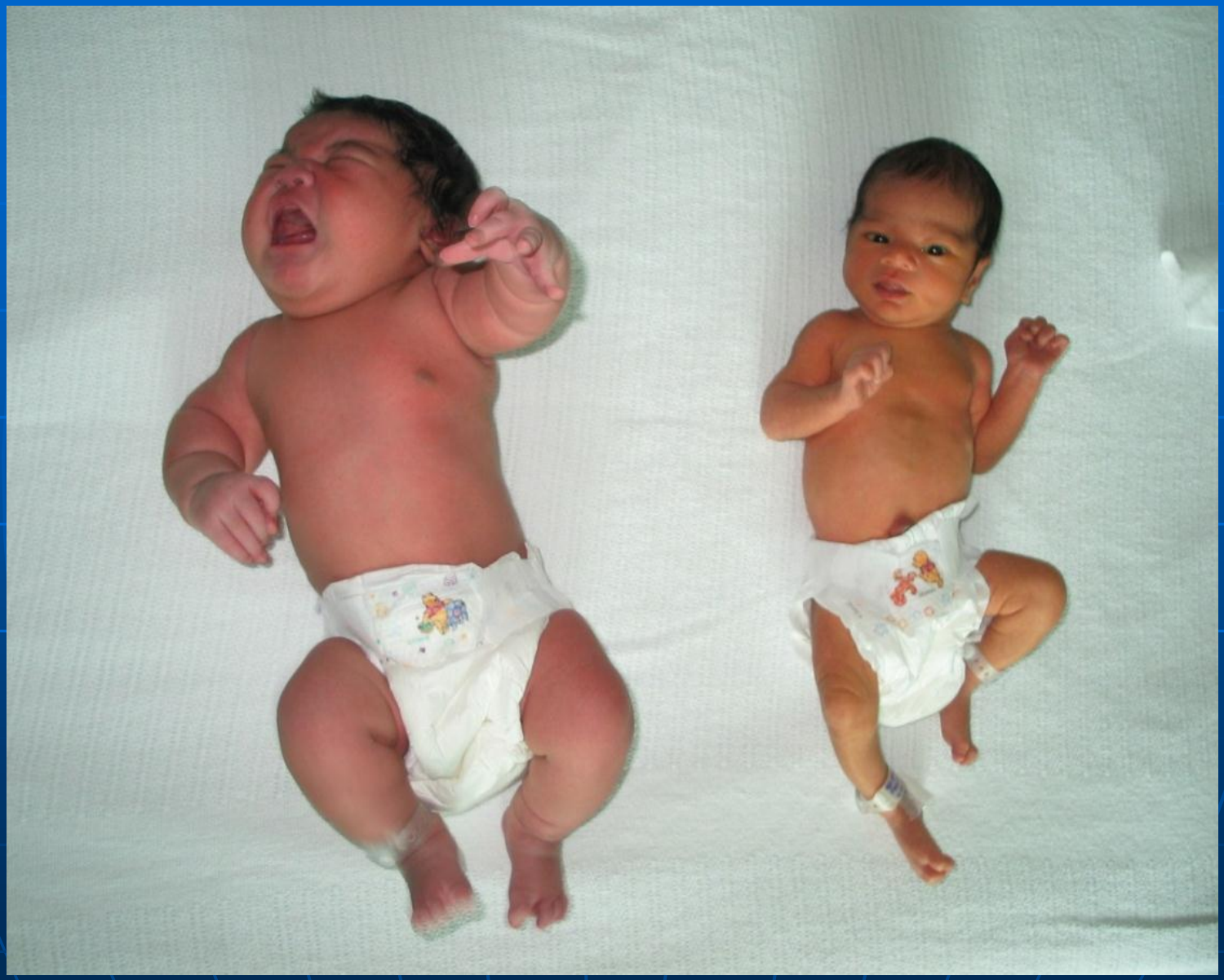
GDM –ACHOIS study

Crowther NEJM 2005 352 2477-86

Prospective study reporting outcomes in 1000 women with "mild" GDM who were randomised to intervention or routine care

Intervention was associated with:

1. Significantly fewer serious adverse pregnancy outcomes
2. No increase in caesarean section rates
3. Improved maternal wellbeing scores at 3 months postpartum



Screening for diabetes in pregnancy

Normally polycose (50g) test around 24-26 weeks of gestation- **1hr glucose>7.8mmol**, an OGTT is done

Pregnant women at high risk of diabetes in pregnancy should be screened earlier

An **Oral Glucose Tolerance Test (OGTT)** should be used to test all High Risk Women as soon as possible

- Previous GDM
- Past obstetric history of macrosomia or stillbirth
- Glycosuria
- High maternal age, >30
- BMI >30
- Polyhydramnios, Evidence of a large baby
- Certain ethnic groups

Oral Glucose Tolerance Test (75g oral glucose)

Fasting serum glucose	Post 2 hours
>5.5	>9.0 *

* Australian guidelines (2hour post glucose >8.0)

Oral GTT
(at booking visit)

If the OGTT is negative, repeat screening should occur at **24-28 weeks** in the **high risk** woman

Higher risk underlying glucose intolerance

- Previous GDM – 70% chance recurrence (?higher)
- Age – over 40 yrs (3% of deliveries NWH)
- Obesity (morbid) – European 35kg/m^2, Polynesian 37kg/m^2, Indian/Asian 32kg/m^2 (5% of deliveries)
- Polycystic ovarian syndrome (35-45% have abnormal glucose tolerance in their 30s)
- Family history – two first degree relatives
- Previous obstetric history – stillbirth, shoulder dystocia, macrosomia >97th percentile, customised
- Glycosuria

Early diagnosis of glucose intolerance

IADPSG Diab Care March 2010

Diagnosis of overt diabetes in pregnancy

- All women or high risk women to be tested at booking
- Fasting glucose ≥ 7.0mmol/l
- HbA1c ≥ 6.5% (48mmol/l)
- Random plasma glucose ≥11.1mmol/l (confirmed)

Diagnosis of early GDM (secondary issue)

- Fasting glucose ≥ 5.1mmol/l and <7.0mmol/l
- No comment on random glucose/HbA1c

Antenatal care of diabetes

When pregnancy is confirmed in diabetics

- Need immediate referral to the Antenatal Diabetes clinic for multidisciplinary input
- Education and ongoing support (e.g. telephone support with specialist nurse)
- Continue basal bolus insulin regimen – need tight control to achieve targets (see below)
- Regular capillary glucose measurements throughout the day

Targets in Pregnancy

Fasting blood glucose	4.0-5 mmol/L
2 hour post-prandial	4.0-6.5 mmol/L
HbA1c	<6.0%

Clinic Assessments

- <28 weeks - 4 weekly
- <36 weeks – 2 weekly
- >36 weeks – weekly

Every visit

- Blood pressure
- Urinalysis (glucose, protein, ketones)
- Weight
- Random BSL

Monthly

- HbA1c

Each Trimester

- Retinal screening
- CBC
- Renal function
- Uric acid
- Thyroid function test

Original Article

Hyperglycemia and Adverse Pregnancy Outcomes

The HAPO Study Cooperative Research Group

In this large, multinational study, glucose levels that were increased during pregnancy but were below levels diagnostic of diabetes were significantly associated with increased risks of birth weight above the 90th percentile and C-peptide levels above the 90th percentile, as well as with other adverse pregnancy outcomes
These results indicate the need to reconsider current thresholds for diagnosing and treating hyperglycemia during pregnancy

N Engl J Med
Volume 358(19):1991-2002
May 8, 2008

HAPO: Hyperglycemia and Adverse Pregnancy Outcome study

Observational study, "low risk" population

OGTT during pregnancy included if

- Fasting ≤ 5.7 mmol/l
- 2-hour ≤ 11.1 mmol/l

and random glucose 34-37 weeks < 9.0 mmol/l

25,505 OGTTs, unblinded 2.9%, dropout 5.6%

Outcomes in 23,325 women analysed

1. Primary cesarean section rates
2. LGA
3. Neonatal hypoglycaemia
4. Cord blood C-peptide

HAPO: Hyperglycemia and Adverse Pregnancy Outcome study

	Intervention	Routine	Adj p value
Preeclampsia	12%	18%	0.02
Gestation	39.0	39.3	0.01
Birthweight	3335 ±551	3482 ±660	<0.001
LGA	13%	22%	< 0.001
SGA	7%	7%	

HAPO

NEJM 2008;358:1991-2002

Overall, low risk population with good outcomes
(Does not include 3% of population with higher levels)

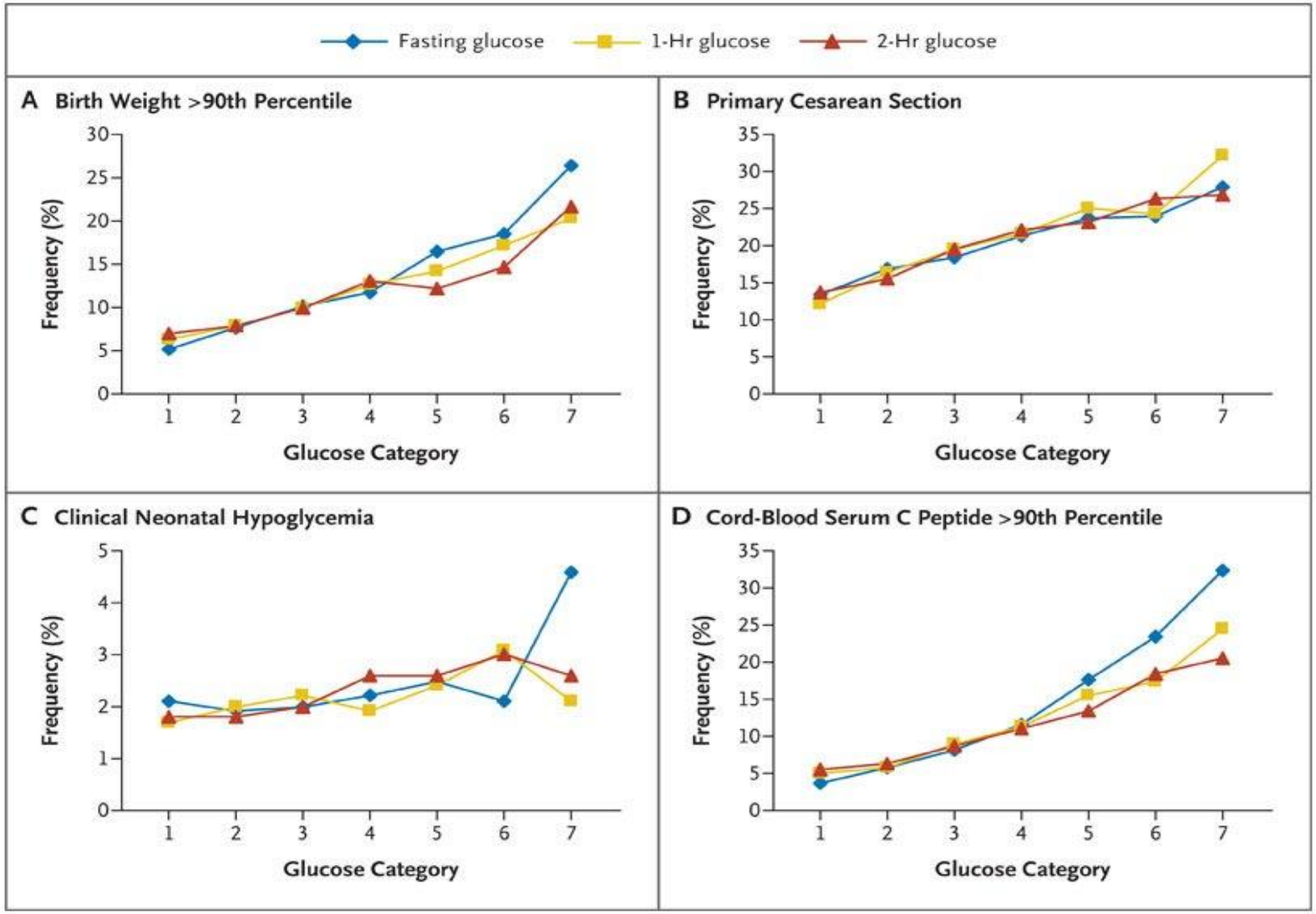
Category	Fasting	1-hr	2-hr
1	<4.2	<5.9	<5.1
2	4.2-4.4	5.9-7.3	5.1-6.0
3	4.5-4.7 (26.6%)	7.4 -8.6	6.1 -6.9
4	4.8-4.9 (11.8%)	8.7-9.5 (15%)	7.0-7.7 (16.2%)
5	5.0-5.2 (8.1%)	9.6-10.7 (8.3)	7.8-8.7 (6.8%)
6	5.3-5.5 (2.9%)	10.8-11.7 (3.5%)	8.8-9.8 (2.6%)
7	≥ 5.6 (0.9%)	≥ 11.8 (1.2%)	≥ 9.9 (1.0%)

HAPO primary outcomes

	FPG Category 1 %	FPG Category 7 %
Birth weight >90th*	5.3	26.3
Primary caesarean	13.3	27.9
Clinical hypoglycaemia	2.1	4.6
Cord C-peptide >90th*	3.7	32.4

* OR >2.0 for outcome once reach category 4-5

Frequency of Primary Outcomes across the Glucose Categories



The HAPO Study Cooperative Research Group. N Engl J Med 2008;358:1991-2002

Glycaemic Aims

So, a reasonable aim is…

- Fasting capillary glucose < 5.0
- 2-hour after beginning of meal <6.5 (6.0)
- (1 –hr level <7.5 (7.0)

But should we accept higher levels ?

Normally grown fetus

May be more aggressive if macrosomic fetus

Diagnosis of GDM in Pregnancy: 75g OGTT

IADPSG Diab Care March 2010

Plasma Glucose	mmol/l	prevalence (%)
fasting	5.1	8.3
1-hr	10.0	14.0
2-hr	8.5	16.1

*GDM = 1 or more values ≥ threshold

HAPO secondary outcomes

A number of secondary outcomes showed a continuous relationship with maternal glucose levels on OGTT at 28 weeks'.

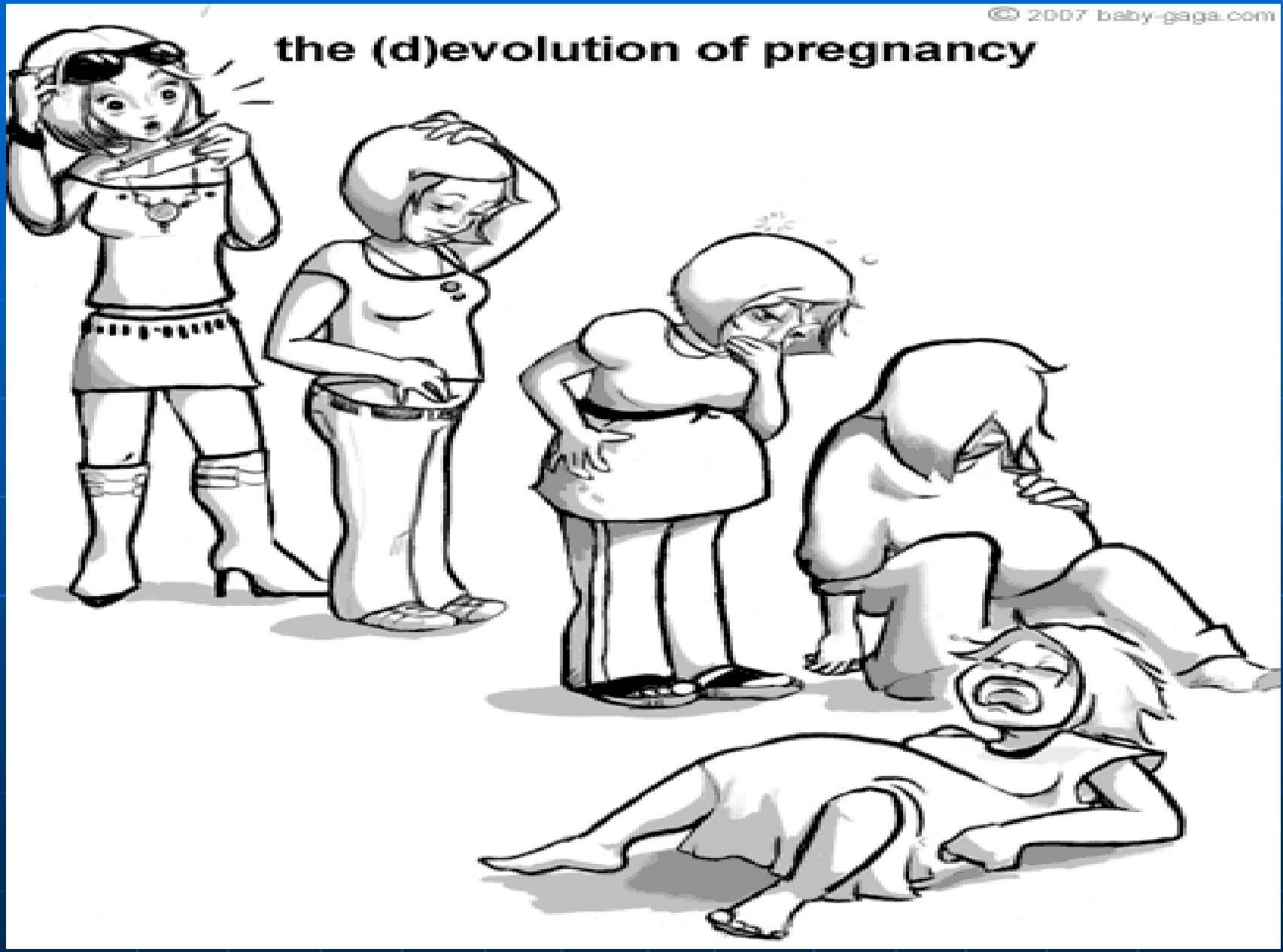
- Preterm birth
- Shoulder dystocia or birth injury
- NICU admission
- Hyperbilirubinaemia
- Maternal preeclampsia
- Neonatal skinfolds

MFM Network trial – treating mild GDM

Landon et al NEJM 2009;361:1339-48

Treating mild GDM significantly reduced

- LGA and neonatal fat mass
- Shoulder dystocia
- Caesarean section
- Hypertensive complications


© 2007 baby-gaga.com
the (d)evolution of pregnancy

GDM – management

AIMS:

- To prevent complications and keep pregnancy "normal"
- To give advice about prevention of type 2 diabetes

1. Education, healthy diet and exercise, postnatal issues
2. Blood glucose monitoring
3. If glucose remains high, start metformin and/or insulin (or glibenclamide?)
4. Careful pregnancy monitoring
5. Address other comorbidities (eg obesity, mental health, social, B12, vitamin D)
6. Long term lifestyle intervention, screening

Medication

Insulin

Individualised treatment, often premeal short-acting analogue, night time intermediate isophane

Level of insulin resistance needs to be recognised

Hypoglycaemia is rarely a major problem for GDM, and type 2 patients

Treatment

- Diet and Exercise
- Insulin- NPH/ Long acting or rapid acting analog insulins
  - Basal-bolus
  - CSII
- Metformin- MIG Trial
- Combination of insulin+Metformin in selected patients

Original Article

Metformin versus Insulin for the Treatment of Gestational Diabetes

Janet A. Rowan, M.B., Ch.B., William M. Hague, M.D., Wanzhen Gao, Ph.D., Malcolm R. Battin, M.B., Ch.B., M. Peter Moore, M.B., Ch.B., for the MiG Trial Investigators

This open-label trial compared insulin with metformin (with supplemental insulin if required) for the treatment of gestational diabetes mellitus

The rates of neonatal complications were similar in the two groups, and more women in the metformin group than in the insulin group reported that they would choose their assigned treatment again

These results provide support for the use of metformin as initial treatment for gestational diabetes in women who require pharmacologic therapy

N Engl J Med
Volume 358(19):2003-2015
May 8, 2008

Metformin – the mother

- Decreases hepatic glucogenesis, free fatty acid levels, results in improved insulin, leptin sensitivity
- Oral, no hypoglycemia, cheaper
- DPP data: young women had equal benefit from metformin vs lifestyle
- MiG data
  - Weight gain: 0.4/0.8 kg vs 2.0 kg in insulin arm
  - Metformin more acceptable than insulin
- Theoretical advantages over glibenclamide

No, I am not planning pregnancy

Case-1

- 28 year old lady with type 2 diabetes comes to see you because she is now 8-10 weeks pregnant.
- She has hypertension, dyslipidaemia and a smoker
- She has normal retinal screening, no current microalbuminuria, has normal creatinine
- She is on Metformin, Glipizide, Accupril, Atorvastatin and Aspirin

What are you going to do?

Answers

1. Find another GP please
2. Stop all her medications and refer her to local Antenatal clinic (ANC)
3. Stop her ACEi, Atorvastatin and refer her to local ANC
4. Refer her for smoking cessation programe
5. Start her on Folic acid and do baseline bloods, refer her for ANC
6. Advise her to monitor SMBG, monitor BP-may need alternative agent, start her on insulin if control is not good.

Diabetes: think about pregnancy

Pre-existing diabetes

- Control
- Complications
- Medications
- Associated health issues
- Plan pregnancy/Contraception

Pre-existing diabetes and pregnancy

Poor diabetes control is associated with birth defects

No exact cutoff, consider all factors

- No diabetes: risk 2-3%
- HbA1c < 7.0%: risk up to 5-6%
- HbA1c > 8.0%: risk 8-10%
- HbA1c > 9.0%: risk 10-20%

Folic acid may reduce risk of anomalies – preconceptual 0.8mg/elevit

?Role for antioxidants

Data hard to interpret, so no "correct" figure

Ace-inhibitors and congenital anomalies

Cooper NEJM 2006;354(23)2443-51

Retrospective database information (>29,000 infants)

- 1985-2000
- Excluded maternal diabetes
- Ace-inhibitor exposure 1st trimester (n=209)
- Compare with other antihypertensives (n=202)

Major congenital anomaly rates

Ace-inhibitors and congenital anomalies

Cooper NEJM 2006;354(23)2443-51

Exposure to ace-inhibitors

Major anomalies:	RR = 2.71 (95th CI 1.72-4.27)
Cardiovascular:	RR = 3.72 (95th CI 1.89-7.30)
CNS:	RR = 4.39 (95th CI 1.37-14.02)

"Exposure to ACE inhibitors in first trimester cannot be considered safe and should be avoided"

Other medications

Lipid lowering statins

- Contraindicated in pregnancy – potential adverse effects in developing fetus (need cholesterol)
- Reports of midline CNS defects, limb reduction
- Cross the placenta but less with pravastatin
- Level of risk unclear

Other lipid lowering agents

- Generally avoid, unless severe hypertriglyceridaemia
- Reports of safe use of fibrates and nicotinic acid

Other medications

Other antihypertensives

- Methyldopa: safe but old-fashoined, frequent administration, side-effects, not used commonly prepregnancy
- Calcium channel blocker (nifedipine, diltiazem (limited data)
- Labetalol or B blocker eg metoprolol (side effects)

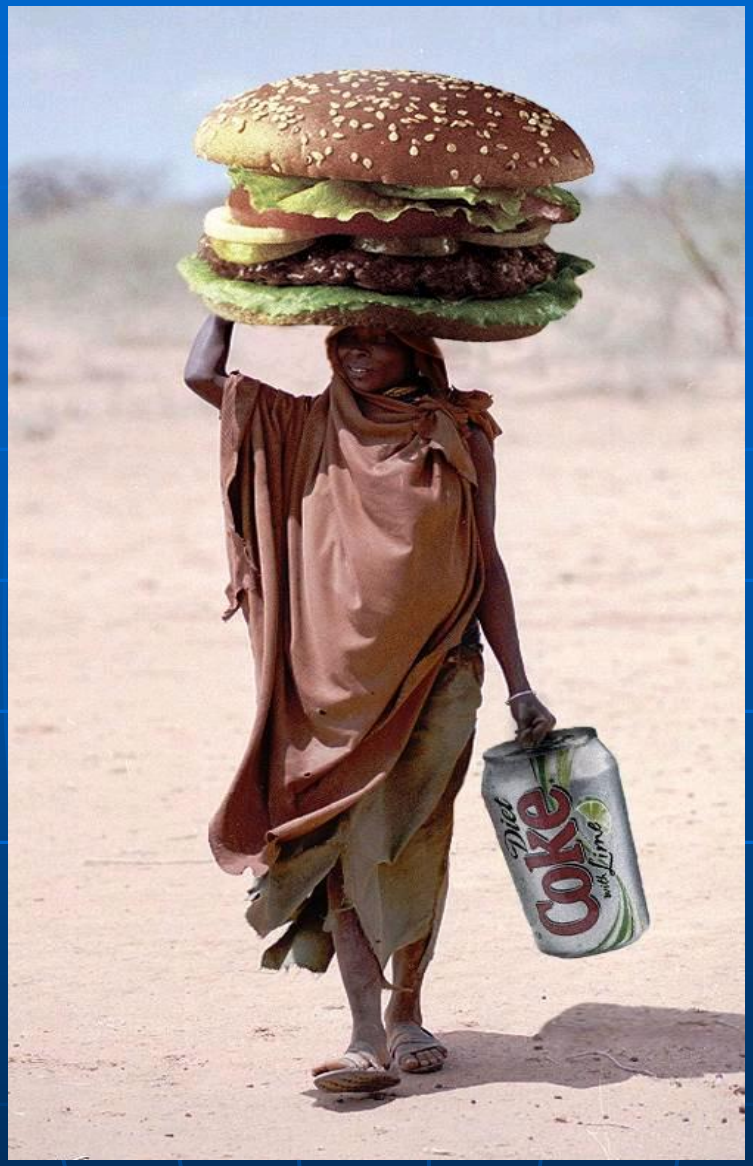
Other medications

Low dose aspirin

SSRI Antidepressants

(fluoxetine, paroxetine, citalopram)

- Outcomes for child better if a depressed woman is treated for her depression
- Citalopram best safety data in pregnancy, next fluoxetine
- Paroxetine issues: may be increased VSDs, higher rates neonatal behavioural issues (shorter-acting, possibly serotonin withdrawal)


Diet
Coke
with lime

Post natal management- GDM

- Breastfeeding for >3 months in obese women with GDM associated with reduction in childhood obesity
- 6weeks post partum oral glucose tolerance test(OGT)
- Subsequent pregnancy- early referral and start testing glucoses
- Annual fasting glucose/2-3 yrly or OGT, depending on other risk factors. Eg: high BMI, family history of DM, certain ethnic groups
- Address CV risk factors

Diabetes and pregnancy: postnatal

Promote breastfeeding

- Aim to maintain reasonable diabetes control, as poor control alters lipid composition of breast milk
- Breastfeeding for >3 months in obese women with GDM associated with reduction in childhood obesity
- Breast feeding alright with metformin (in breast milk low levels) glibenclamide, glipizide (not detected in breast milk)

Regain hypoglycaemic awareness

Contraception – risk vs benefits

Diabetes and pregnancy: postnatal

- Type 2 diabetes women have treatment stopped during delivery then they are reassessed postpartum. Most have metformin restarted, some require other oral agent and/or insulin
- Reintroduce ACEi, Lipid lowering therapy, Aspirin
- Retinal screening
- Contraception

A 28 yr old European woman presents at 6 weeks. She has a BMI of 37 kg/m^2. She had previous GDM and a normal postpartum OGTT 2 years earlier

TRUE OR FALSE:

a. A random plasma glucose of 6 mmol/l is normal

b. If her HbA1c is 40 mmol/mol (5.8%) she can wait and be screened at 28 weeks'

c. If an OGTT at 16 weeks is normal she should have a repeat OGTT at 32 weeks

d. She should be advised to gain 6-9 kg in pregnancy

Weight gain in pregnancy

Institute of Medicine 2009

BMI (kg/m^2)	Weight gain (kg)
<18.5	12.7-18
18.5-24.9	11.4-16
25.0-29.9	6.8-11
30.0 or more	5-9

Woman with diabetes planning for pregnancy

- 32 yr old, type 2 diabetes for 5 yrs
- Mild microalbuminuria, ACR 6, Cr 60, eGFR> 90
- Quinapril 20mg bid for HT
- Mild retinopathy
- Dyslipidaemia- on simvastatin 40mg daily
- Current HbA1C 8.4%, on Metformin 850mg bid, Glipizide 10mg bid
- Smoker

What will you do?

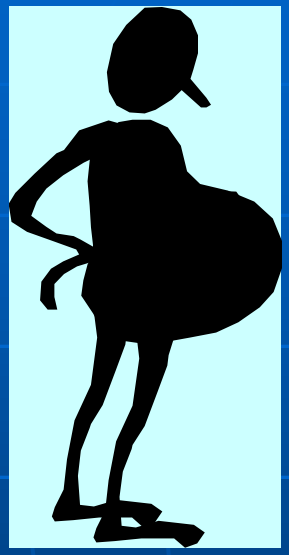
- Advise not to attempt for pregnancy
- Refer for pre-pregnancy counseling
- Start Folic acid,
- Continue OHAs (metformin, Glipizide), do you have to stop any of them?
- Stop quinapril
- Stop simvastatin
- Refer for smoking cessation

- What alternative agents can be used for hypertension?

Management

- Aim for near normal glycaemia- A1c <6%
- Can continue current oral agents, but may need insulin-evening NPH insulin or basal bolus regime
- Start folic acid
- Stop Quinapril, substitute with Methyl dopa, Diltiazem, or Labetalol
- Refer for smoking cessation
- Baseline urine microalbumin, Cr, LFTs, TSH, FBC and up to date retinal screening
- Stop simvastatin
- Aspirin- if vascular risk factors
- Up to date retinal screening

Pregnancy is a window into a woman's future health……and her offspring's health



Maternal diabetes

20-60% will develop type 2 DM within 5-16 years

Metzger Arch Dis Child 1990
Care 1995

Dabelea Diabetes 2000 JMFM 2000

Silverman Diabetes

↑obesity at 6 yr

33% IGT at 12 yr

Higher BMI
2.6 kg/m²

Risk of Diabetes
Odds ratio: 3.7

Take home Messages

- Facilitate pre-pregnancy planning in women with diabetes
  - Optimal glycaemic, BP control
  - Folic acid
- Ensure 6 weeks post partum OGTT in women who have had GDM and subsequent follow-up re:long term risk of developing type 2 DM
- Know the appropriate medications for pregnancy

Thank you.

- Like to acknowledge Dr Janet Rowan, Obstetric Physician, NWH